Herpes Zoster (Shingles) and Postherpetic Neuralgia

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On completion of this article, you should be able to (1) recognize the common presentation of herpes zoster, (2) summarize appropriate treatment for acute herpes zoster and postherpetic neuralgia, and (3) select patients for whom herpes zoster vaccine is appropriate.

Herpes zoster (HZ), commonly called *shingles*, is a distinctive syndrome caused by reactivation of varicella zoster virus (VZV). This reactivation occurs when immunity to VZV declines because of aging or immunosuppression. Herpes zoster can occur at any age but most commonly affects the elderly population. Postherpetic neuralgia (PHN), defined as pain persisting more than 3 months after the rash has healed, is a debilitating and difficult to manage consequence of HZ. The diagnosis of HZ is usually made clinically on the basis of the characteristic appearance of the rash. Early recognition and treatment can reduce acute symptoms and may also reduce PHN. A live, attenuated vaccine aimed at boosting immunity to VZV and reducing the risk of HZ is now available and is recommended for adults older than 60 years. The vaccine has been shown to reduce significantly the incidence of both HZ and PHN. The vaccine is well tolerated, with minor local injection site reactions being the most common adverse event. This review focuses on the clinical manifestations and treatment of HZ and PHN, as well as the appropriate use of the HZ vaccine.

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HZ = herpes zoster; PHN = postherpetic neuralgia; TCA = tricyclic antidepressant; VZV = varicella zoster virus

Herpes zoster (HZ), commonly called *shingles* from the Latin *cingulum*, meaning belt,[1] is a distinctive syndrome caused by reactivation of varicella zoster virus (VZV). The risk of HZ increases with age; approximately half of all cases occur in persons older than 60 years. One of the most common and debilitating sequelae of HZ is postherpetic neuralgia (PHN), defined as pain persisting more than 3 months after the rash has healed.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Herpes zoster is a painful, blistering skin eruption in a dermatomal distribution. After primary infection with varicella (ie, chicken pox), the virus persists asymptomatically in the ganglia of sensory cranial nerves and spinal dorsal root ganglia. As cellular immunity to VZV decreases with age or because of immunosuppression, the virus reactivates and travels along the sensory nerves to the skin, causing the distinctive prodromal pain followed by eruption of the rash. It is estimated that approximately 1 in 3 people will develop HZ during their lifetime, resulting in an estimated 1 million episodes in the United States annually.[2] Herpes zoster can occur at any age but is generally less severe in children and young adults, with the greatest morbidity and mortality seen in older adults and in immunocompromised patients. A recent population-based study in Olmsted County, Minnesota, found that the incidence of HZ was 3.6 per 1000 patient-years.[3] In that study, the incidence of HZ and the rate of HZ-associated complications increased with age, with 68% of cases occurring in those aged 50 years and older. Prodromal symptoms that herald HZ include pruritus, dysesthesia, and pain along the distribution of the involved dermatome. This pre-eruptive pain may precede the rash by several days and may be mistaken for myocardial infarction, biliary or renal colic, pleurisy, dental pain, glaucoma, duodenal ulcer, or appendicitis, leading to misdiagnosis and potentially mistreatment. In rare instances, the nerve pain is not accompanied by a skin eruption, a condition known as *zoster sine herpete*. The classic skin findings are grouped vesicles on a red base in a unilateral, dermatomal distribution (Figure 1). However, the lesions of HZ progress through stages, beginning as red macules and papules that, in the course of 7 to 10 days, evolve into vesicles and form pustules and crusts (scabs) (Figure 2). Complete healing may take more than 4 weeks.

The localization and distribution of the skin findings are distinctive. Typically, HZ is unilateral, does not cross the midline, and is localized to a single dermatome of a single sensory ganglion (adjacent dermatomes are involved in 20% of cases).[4] The most common sites are the thoracic nerves and the ophthalmic division of the trigeminal nerve. Herpes zoster ophthalmicus, which occurs in 10% to 20% of HZ episodes,[5] can involve the entire eye, causing keratitis, scarring, and vision loss. An early sign of this condition is vesicles on the tip, side, or root of the nose (Hutchinson sign). Herpes zoster of the second and third divisions of the trigeminal nerve may produce symptoms and lesions in the

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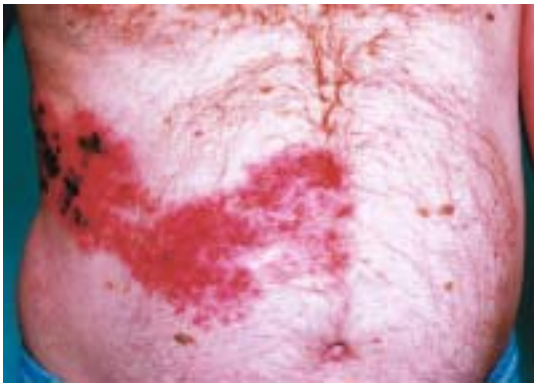

FIGURE 1. The classic skin findings of herpes zoster are grouped vesicles on a red base in a unilateral, dermatomal distribution.

mouth, ears, pharynx, or larynx. Ramsay Hunt syndrome, ie, facial paralysis and lesions of the ear (zoster oticus) that are often accompanied by tinnitus, vertigo, and deafness, results from involvement of the facial and auditory nerves. Some cases of Bell palsy may be a form of zoster sine herpete.

Disseminated HZ occurs primarily in immunocompromised patients; it usually presents with a dermatomal eruption followed by dissemination but may also present with a diffuse varicella-like eruption. Systemic dissemination may accompany the skin changes with involvement of the lung, liver, and brain. Visceral dissemination is associated with a mortality rate of 5% to 15%, with most deaths attributable to pneumonia.[6,7] The neurologic complications of HZ may include acute or chronic encephalitis, myelitis, aseptic meningitis, polyradiculitis, retinitis, autonomic dysfunction, motor neuropathies, Guillain-Barré syndrome, hemiparesis, and cranial or peripheral nerve palsies.[8,9] More common complications include bacterial superinfection by *Staphylococcus aureus* or *Streptococcus pyogenes*, scarring, and hyperpigmentation.

Herpes zoster is usually diagnosed clinically by the prodromal pain, characteristic rash, and distinctive distribution. However, a group of vesicles, especially if located by the mouth or genitals, can represent other possibilities. The differential diagnosis for HZ includes herpes simplex virus, impetigo, candidiasis, contact dermatitis, insect bites, autoimmune blistering disease, dermatitis herpetiformis, and drug eruptions. Although shell vial viral culture remains the criterion standard test with which other diagnostic tests are compared, detection of viral DNA by polymerase chain reaction, when available, is the most useful test because it is sensitive and specific and results can be obtained within a few hours.[10] Other tests that can be used to support the diagnosis are direct fluorescent antibody staining, immunoperoxidase staining, histopathology, and Tzanck smear.

Herpes zoster lesions contain high concentrations of VZV, which can be spread by contact and by the airborne route and which can cause primary varicella in exposed, susceptible persons. Less contagious than primary varicella, HZ is only contagious after the rash appears and until the lesions crust.[11] Risk of transmission is reduced further if lesions are covered.

TREATMENT OF ACUTE HZ

The goal of treatment during the acute episode is to control symptoms and prevent complications. Treatment options include antiviral therapy, corticosteroids, and pain medications.

Antivirals

Acyclovir, famciclovir, and valacyclovir are nucleoside analogues that inhibit replication of human herpes viruses, including VZV. When taken orally, these agents reduce the duration of viral shedding, hasten rash healing, reduce the severity and duration of acute pain, and reduce the risk of progression to PHN.[12,13] Because antivirals are safe and well tolerated, they should be considered for all patients with HZ. Antiviral treatment is specifically recommended for patients older than 50 years, those who have moderate or severe pain or rash, and those with involvement of nontruncal dermatomes (eg, the face). In clinical trials, treatment has been initiated within 72 hours of rash onset, an arbitrarily selected time point. Such a rapid initiation of treatment is often not feasible in clinical practice. Although the benefits of treat-

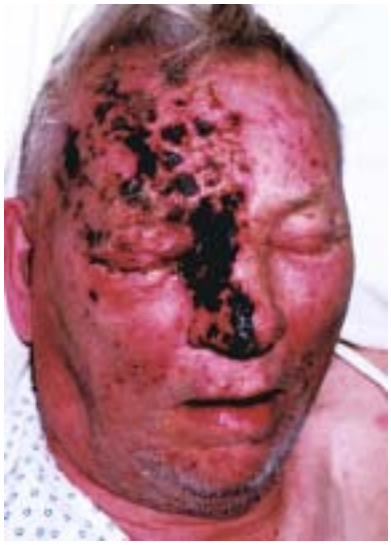

FIGURE 2. The lesions of herpes zoster progress through stages, beginning as red macules and papules that, in the course of 7-10 days, evolve into vesicles and form pustules and crusts (scabs). A common site is the distribution of the ophthalmic division of the trigeminal nerve.

TABLE 1. **Treatment of Acute Herpes Zoster**[a]

Class of agent and usual dose	Patients in whom treatment is indicated	Comments
Antivirals[b]		
Famciclovir: 250 mg orally 3 times daily for 7 d Valacyclovir: 1 g orally 3 times daily for 7 d Acyclovir: 800 mg orally 5 times daily for 7 d In immunocompromised patients/disseminated disease: acyclovir, 10 mg/kg intravenously every 8 h until resolution of cutaneous/visceral disease	All who present within 72 h of rash onset Consider antivirals in those who present >72 h after rash onset if they have the following characteristics: Age >50 y Immunocompromised status Severe pain at presentation High-risk lesions (involving tip of nose/eye)	Antivirals reduce both acute symptoms and subsequent risk of PHN Oral acyclovir is the least expensive drug regimen ($20 for a 7-d course vs $80-$90 for a 7-d course of valacyclovir or famciclovir)
Glucocorticoids		
Prednisone: 60 mg orally for 7 d, then taper for next 2 wk	Those who are older and/or those with severe pain as long as no contraindications exist	Corticosteroids have no effect on the subsequent development of PHN and should be used with antivirals, never alone; significant adverse effects are possible
Pain medications		
Tramadol Oxycodone/acetaminophen	Most will require some type of pain medication	Opioids should be used with caution in elderly patients Prophylactic laxatives and stool softeners should be considered when prescribing opioids

[a] PHN = postherpetic neuralgia
[b] Recommended antiviral dosages are for persons with normal renal function. Dosages need to be adjusted on the basis of creatinine clearance.

ment that is begun later have not been studied, antiviral treatment should be considered even in patients who present more than 72 hours after rash onset, particularly in the presence of new vesicle formation or complications. Valacyclovir and famciclovir are generally more convenient for outpatient treatment because they are more bioavailable and hence require less frequent dosing than acyclovir (Table 1). Immunocompromised patients are at greater risk of complications and may require intravenous antiviral therapy.

Corticosteroids

Corticosteroids do not have any effect on PHN. In combination with antiviral therapy, they modestly reduce the severity and duration of acute symptoms.[14,15] Corticosteroids are associated with a considerable number of adverse effects and hence should be used only in patients with severe symptoms at presentation or in whom no major contraindications to corticosteroids exist.

Analgesics

Acute pain will be reduced by antiviral drugs, but patients will generally also require analgesics. Nonsteroidal anti-inflammatory drugs are usually ineffective, and opioids may be required. All the agents discussed for PHN (see Postherpetic Neuralgia) can also be used for pain associated with acute HZ.

POSTHERPETIC NEURALGIA

Postherpetic neuralgia is a debilitating complication of HZ. The risk of PHN after HZ increases with age. In a large population-based study, the rate of PHN (defined as at least 90 days of documented pain) increased from 5% in those younger than 60 years to 10% in those aged 60 to 69 years and to 20% in those aged 80 years or older.[3] The pain results in large part from damage to the sensory nerves, causing neuropathic pain. The pain is often intermittent and not correlated with external stimuli. Paradoxically, areas of the skin that lack normal sensitivity to touch may be associated with increased pain. Light touch or the brush of clothing is sometimes perceived as being painful, a phenomenon called *allodynia*. It is not uncommon for the pain of PHN to interfere with sleep and recreational activities and to be associated with clinical depression.

Many patients do not understand why their pain lasts after the rash has healed. Some fear that they are imagining the symptoms or that their complaints represent a weakness in character. Patients should be reassured that their symptoms are real and represent the unseen and persistent damage to the sensory nerves.

Unfortunately, there is no intervention that reliably relieves the pain of PHN. Effective therapy often requires multiple drugs. Therefore, it is essential to undertake treatment in a systematic fashion that will allow appropriate assessment of both benefit and adverse effects for each drug. If 2 medications are started simultaneously and the patient has an adverse reaction, it will often be necessary to eliminate both medications. Another general principle is to have patients begin a medication at a very low dose and increase the dose gradually until either analgesia or adverse effects are noticed. Beginning with a dose that is lower than the anticipated effective level increases the likelihood of a beneficial effect before the onset of adverse effects. It is helpful to keep detailed records of

medication trials, including dosage, benefit, and adverse effects.

It is usually best to begin with a medication that either has the fewest adverse effects or that is perhaps associated with desirable side effects. For example, topical medications are almost always free of systemic adverse effects. Conversely, tricyclic antidepressants (TCAs) often have sedating side effects that may be helpful for patients who suffer from insomnia. Patients often benefit from the simultaneous use of several medications working together synergistically. It is useful to choose 1 medication from each distinctive class before using more than 1 medication from the same class. For the purposes of this clinical review, the classes of medication will be divided into the following: topical agents, antidepressants, anticonvulsives, and opioids.

Topical Agents

A variety of topical agents have been shown to be effective for PHN. Topical lidocaine patches are particularly effective for patients with allodynia.[16] Lidocaine works by decreasing small fiber nociceptive activity, and the patch itself serves as a protective barrier from the brush of clothing. Capsaicin is another topical agent that has shown efficacy in randomized clinical trials.[17,18] However, the burning sensation associated with the application of capsaicin often limits its clinical use. Patients should be advised that the burning sensation decreases with continued use of capsaicin. Topical therapy with capsaicin should be continued for at least 4 weeks because it may take that long for substantial pain relief to occur. Patients should expect some amount of discomfort before deriving benefit. A variety of other compounded pharmaceutical agents have been reported for use in PHN. Although clinical evidence is lacking to recommend any one of these products, topical medications usually result in very low systemic absorption and thus have relatively few adverse effects.

Antidepressants

Tricyclic antidepressants are the criterion standard for relieving the pain of PHN. Multiple clinical studies have shown the efficacy of nortriptyline and amitriptyline, the most commonly used members of this class.[19] Unfortunately, TCAs are often associated with a variety of anticholinergic adverse effects, sedation, and potential cardiac dysrhythmias. Patients who are unable to tolerate TCAs may do better with selective serotonin and norepinephrine reuptake inhibitors, such as duloxetine or venlafaxine. Although less effective than TCAs, the selective serotonin and norepinephrine reuptake inhibitor antidepressants offer efficacy for both pain and depression with fewer adverse effects. The selective serotonin reuptake inhibitor antidepressants effectively relieve depression symptoms but they do not specifically relieve neuropathic pain. Nevertheless, some patients with chronic pain of PHN will experience clinical depression, and the use of a selective serotonin reuptake inhibitor antidepressant can be useful for the management of their depressive symptoms.

Anticonvulsants

Several anticonvulsants are effective against neuropathic pain. The newer-generation anticonvulsant drugs, such as pregabalin and gabapentin, have fewer adverse effects and require less hematologic monitoring than older anticonvulsants, such as carbamazepine and valproic acid. Pregabalin[20] and gabapentin[21] have both been shown to relieve the pain of PHN. Although both of these drugs work at the same receptor, pregabalin has the advantage of a more predictable and linear pharmacokinetic profile. Other anticonvulsant medications work at different receptors, providing a reasonable justification for trying other drugs if success is not achieved with the first trial.

Opioids

The role of opioids in patients with PHN is controversial. Their long-term use presents risks of sedation, mental clouding, and even abuse or diversion. However, opioids are particularly safe in the context of systemic cardiac, renal, and hepatic adverse effects. Because elderly people bear the overwhelming burden of PHN and also have comorbidities that may limit the use of other medications, opioids may have a role in the treatment of these patients. Mixed μ-opioid agonists and norepinephrine reuptake inhibitors such as tramadol may be good choices for patients with PHN, especially for those with risk factors for substance abuse. Other reasonable options include oxycodone with acetaminophen, or morphine. When prescribing opioids, clinicians should recommend prophylactic constipation therapy from the outset in the form of a stool softener and laxative. More invasive therapies have been proposed for PHN and include electrical stimulation of the thalamus, anterolateral cordotomy, cryotherapy of the intercostal nerves, and ablation of the dorsal roots using pulsed radiofrequency; however, limited data exist to support these therapies. Patients should be referred to a pain medicine specialist before considering these more aggressive treatments. Referral to a pain medicine specialist may also be helpful when drug-drug interactions make management of analgesics more challenging. The commonly used agents for treatment of PHN are summarized in Table 2.

PREVENTION

In 2006, a vaccine to prevent HZ received approval by the Food and Drug Administration. Zostavax (Merck,

TABLE 2. **Management of Postherpetic Neuralgia**[a]

Class of drug	Advantages	Disadvantages and adverse effects	Suggested dosing[b]	Comments
Topical agents	Lidocane and capsaicin have minimal systemic adverse effects	On initial use, capsaicin can cause a burning sensation, which usually resolves with repeated use	Lidocaine: 5% patch; apply up to 3 patches at a time to affected area; use up to 12 h in a 24-h period Capsaicin: 0.075% cream; apply at least 3 times daily[c]	Less frequent use of capsaicin decreases efficacy
Antidepressants				
TCAs	Best for pain relief May help with sleep disturbance	Associated with considerable drowsiness, anticholinergic adverse effects, weight gain, and risk of cardiac arrhythmias	Nortriptyline/amitriptyline: start at 10-20 mg/d; increase dose in 10 mg increments every 3 to 5 d until satisfactory pain relief is achieved or intolerable adverse effects occur, to maximum of 100 mg/d[c]	Use with caution in elderly patients, especially in patients with BPH Recommend medicine at bedtime to help with sleep
SNRIs	Good for pain relief	SNRIs are less effective at alleviating pain but have a better adverse effect profile than TCAs. Adverse effects include nausea and dizziness	Venlafaxine: start at 37.5 mg/d; increase dosage to a maximum of 225 mg/d[c] Duloxetine: start at 20 mg at bedtime; increase by 20 mg every 5 d to a maximum of 60 mg/d[c]	Nausea associated with SNRIs can be reduced by taking after eating
Anticonvulsants	Gabapentin and pregabalin have better adverse effect profile than older agents	Dizziness, somnolence, weight gain, and peripheral edema	Gabapentin: 300 mg on day 1, 300 mg twice daily on day 2, and 300 mg 3 times daily on day 3; may increase dosage up to 1800 mg/d (divided in 3 doses) Pregabalin: 75 mg/d at bedtime; increase by 75 mg every 5 d to maximum of 300 mg twice daily	Taper gradually over at least 1 wk to prevent withdrawal symptoms No advantage to dosing pregabalin more frequently than twice daily
Opioids	Fewest cardiac adverse effects May help with sleep disturbance	Sedation Constipation Abuse or diversion potential	Various agents can be used, titrated to pain relief Suggested starting doses Oxycodone: 5 mg every 4-6 h; increase by 5- to 10-mg increments as needed to 40 mg/d Tramadol: start at 25 mg twice daily; increase every 3 d to a maximum of 200 mg/d	Include prophylactic laxative and stool softener when prescribing opioids Medications compounded with acetaminophen increase efficacy and sometimes allow for prescribing under less regulation

[a] BPH = benign prostatic hypertrophy; SNRI = selective serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.
[b] All dosages are for patients with normal renal/hepatic function. Doses may need to be adjusted in patients with renal/hepatic insufficiency.
[c] Not a Food and Drug Administration–labeled indication.

Whitehouse Station, NJ) is a live, attenuated vaccine that contains the same strain of virus (Oka/Merck) as the varicella vaccines (Varivax, Proquad; Merck, Whitehouse Station, NJ). In a double-blind, randomized, placebo-controlled trial involving approximately 38,000 healthy adults older than 60 years, the vaccine reduced the incidence of HZ by 51%, the burden of illness from HZ by 61%, and the risk of PHN by 66%.[22] The vaccine was most effective in those aged 60 to 69 years; efficacy persisted for at least 4 years after vaccination. Patients enrolled in the study continue to be followed up to estimate how much longer the protection afforded by the vaccine lasts. The Advisory Committee on Immunization Practices recommends routine vaccination of all adults 60 years and older with 1 dose of HZ vaccine, whether or not they have a history of HZ.[2] Because people in this age group can be presumed to have been exposed to varicella, there is no need to check varicella serology before administration of HZ vaccine, even in those who do not remember having chicken pox. The adverse effects of the vaccine are mild and usually consist of erythema, pain, and pruritus at the injection site. Systemic adverse effects are rare and consist of headache and fever. It is important to remember that the HZ vaccine is not interchangeable with the varicella vaccine.

Antivirals active against VZV (acyclovir, famciclovir, and valacyclovir) should not be taken 24 hours before and 14 days after receiving vaccine. The HZ vaccine can be given simultaneously with inactivated vaccines, such as influenza or pneumococcal or tetanus vaccines, or at any interval before or after their administration. Unlike other live vaccines, the HZ vaccine can be administered at any time before, during, or after administration of blood or

TABLE 3. **Herpes Zoster Vaccine Use in Immunocompromised Persons**[a]

Condition/Therapy	Recommendations
Impaired humoral immunity (eg, hypogammaglobulinemia)	Vaccine can be administered
Leukemia, lymphoma, or other hematologic malignancy involving bone marrow or lymphatic system	Vaccine contraindicated during active disease or treatment Vaccine can be administered if patient's disease is in remission, provided that the patient has not received chemotherapy or radiation in previous 3 mo
Impaired cell-mediated immunity, including human immunodeficiency virus infection with CD4 count ≤200 cells/mm^3 or ≤15% of total lymphocytes	Vaccine contraindicated
Hematopoietic stem cell transplant recipients	Consider vaccine on case-by-case basis Wait at least 24 mo after transplant
Corticosteroid therapy	Vaccine can be administered if patient has been taking systemic corticosteroids <14 d or at a dosage of <20 mg/d of prednisone equivalent Inhaled/topical/intra-articular corticosteroids are not a contraindication to vaccine
Recombinant immune modulators (eg, infliximab, adalimumab, etanercept)	Defer vaccine for at least 1 mo after end of therapy
Other immunosuppressive medication	Vaccine can be given with low-dose treatment Methotrexate ≤0.4 mg/kg/wk Azathioprine ≤3 mg/kg/d 6-Mercaptopurine ≤1.5 mg/kg/d

[a] For more detailed information on the recommendations of the Advisory Committee on Immunization Practices, see *MMWR Recomm Rep.*[2]

other antibody-containing blood product. Transmission of vaccine strain virus from vaccine recipients to susceptible contacts has not been documented thus far, and transmission is less likely than from patients who receive varicella vaccine. However, it would be prudent for those who develop a vaccine-related rash to avoid close contact with susceptible persons until the rash heals.

The vaccine is relatively expensive, costing approximately $160, and actual charges to the patient are usually higher.[23] Coverage for the vaccine varies among private insurers. For patients older than 65 years, the vaccine is covered by Medicare Part D as a prescription drug. Patients will have varying co-pays for the vaccine depending on their drug plan (unlike influenza and pneumococcal vaccines that are fully covered as preventive measures). The vaccine administration fee (ranging from $10-$30) charged by physicians' offices is also not covered by Medicare. Cost needs to be discussed with patients before administration of the vaccine. Availability of the vaccine has been limited during recent months because the manufacturer has been unable to keep up with demand. During the shortage, the Centers for Disease Control and Prevention has recommended that the vaccine be reserved for patients anticipating immunosuppression in the near future. The shortage is expected to ease in 2009.

The VZV vaccine is contraindicated in the setting of severe immunosuppression because it is a live vaccine. Specific issues related to the use of HZ vaccine in immunosuppressed persons are addressed in Table 3.

CONCLUSION

The incidence of HZ and PHN increases with increasing patient age. Early diagnosis of HZ and treatment with antiviral medications decreases the risk of PHN. Postherpetic neuralgia is very difficult to treat. Even with the use of a variety of medications and referral to a pain specialist, pain relief may be incomplete. Prevention through a newly licensed HZ vaccine is an exciting development.

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CME Questions About Herpes Zoster and Postherpetic Neuralgia

1. Which *one* of the following statements about herpes zoster (HZ) is *true*?
   a. Risk decreases with increasing age
   b. It presents as a disseminated rash
   c. Patients with HZ are infectious for 48 hours before the onset of the rash
   d. It usually affects the trunk or face
   e. It is associated with pain that is usually self-limited and mild

2. In which *one* of the following sites should HZ involvement prompt referral to an ophthalmologist?
   a. Ear
   b. Nose
   c. Lips
   d. Throat
   e. Scalp

3. Which *one* of the following treatments for HZ has been shown to *decrease* the risk of postherpetic neuralgia (PHN)?
   a. Antivirals
   b. Corticosteroids
   c. Topical lidocaine
   d. Anticonvulsants
   e. Opioids

4. Which *one* of the following medications presents the *least* risk for an elderly patient with PHN?
   a. Amitriptyline
   b. Nortriptyline
   c. Carbamazepine
   d. Tramadol
   e. Gabapentin

5. Per the recommendations of the Advisory Committee on Immunization Practices, HZ vaccine is indicated for which *one* of the following patients?
   a. A 49-year-old man awaiting kidney transplant
   b. A 36-year-old woman with newly diagnosed breast cancer
   c. A 61-year-old patient with a 10-year history of type 2 diabetes mellitus
   d. A 61-year-old patient taking 40 mg/d of prednisone for temporal arteritis
   e. A 22-year-old man with human immunodeficiency virus infection and a CD4 count of 50 cells/mm^3 of blood

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

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